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# IUPHAR-DB: An Open-Access, Expert-Curated Resource for Receptor and Ion Channel Research

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**ABSTRACT:** This contribution highlights efforts by the International Union of Basic and Clinical Pharmacology (IUPHAR) Nomenclature Committee (NC-IUPHAR) to classify human receptors and ion channels, to document their properties, and to recommend ligands that are useful for characterization. This effort has inspired the creation of an online database (IUPHAR-DB), which is intended to provide free information to all scientists, summarized from primary literature by experts.

**KEYWORDS:** Drug target, chemical tool, GPCR, ion channel, biocuration, database

The recent explosion in data generation from high-throughput studies (ligand-screening, genomic and proteomic data sets) as well as the sheer volume of scientific literature represents an enormous, largely untapped data mine relevant to drug discovery and drug target research in neuroscience. Maximizing the benefits of the information requires researchers to keep abreast of new developments in an increasingly complex area and to quickly extract their meaning. There is a fundamental need for resources which distill available data into an easy-to-digest format, identifying the most important information, standardizing it, integrating it with other, often disparate, data sources, placing it in context, and making authoritative recommendations about the data. This time intensive process forms a significant part of what is now referred to as “data curation”, which we believe is essential to building trusted public scientific information resources.

In today's interdisciplinary information age, basic pharmacological research can no longer be considered separate from, but must form an integral part of, the rational drug discovery cycle. Discoveries from basic science are essential inputs to the drug development process, and pharmaceutical companies are increasingly recognizing the value of sustained academic and collaborative precompetitive research into drug targets.<sup>1</sup> Such a multidisciplinary, translational approach to pharmacology and drug discovery would benefit from having community-developed public-domain knowledge bases and repositories for information from literature.<sup>2</sup> These would ideally provide details and recommendations on all factors that may influence drug targets and their interactions with ligand molecules, at species, individual, and cellular levels. This would expand the available target information, defining drug targets in their biological contexts and increasing awareness of the range of targets which interact with each compound. Large data warehouses of chemical information such as PubChem<sup>3</sup> and ChemSpider<sup>4</sup> and medicinal chemistry databases such as ChEMBL<sup>5</sup> exist to catalog the vast chemistry space. However, there remains a need for focused public-domain resources to identify the most commonly used chemical tools and drugs and connect them to data on biological targets and clinical relevance.

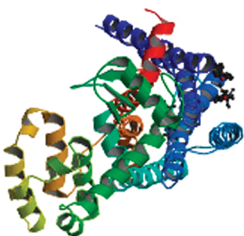
The International Union of Basic and Clinical Pharmacology (IUPHAR) Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), a voluntary, nonprofit association, issues guidelines for the classification and naming of human receptors and ion channels.<sup>6</sup> Their mission is to provide recommendations for pharmacology (e.g., refs 7 and 8), to distill relevant data from literature on receptors and their properties, to disseminate the information publicly, and to provide a platform for experts to discuss current issues. Their work is communicated through an online database, IUPHAR-DB (<http://www.iuphar-db.org>), which is intended to provide free information on human drug targets to scientists anywhere in the world.<sup>9</sup> IUPHAR-DB is driven by an expert curation model relying on NC-IUPHAR's >60 subcommittees of international experts (numbering ~700 individuals from academia and industry).

By engaging experts in the data curation process, NC-IUPHAR is trying to address one of the significant issues in drug discovery today: that of identifying the repertoire of human drug targets. In this endeavor, it is essential to recognize all of the factors that can influence receptor structure, function, expression, and pharmacology. Drug targets are defined in a broader sense than “single gene products” to encompass other variables which affect function. Factors that contribute to the definition of a unique target include the particular sequence variant(s) present; specific tissue and subcellular location; a given combination of subunits, cofactors, and ligands; presence of post-translational modifications; pathophysiological context; and the downstream signaling pathway being initiated. These can vary across species, individual, tissue, developmental stage, and disease to give rise to a much more diverse range of potential drug targets than are specified at the gene level. Moreover, there is increasing evidence that ligand selection can influence the specific downstream pathways affected and therefore the functions mediated (for a recent review, see ref 10).

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Selected 3D Structures ?						
		Description:	Crystal structure of chimeric $\beta$ 2-adrenergic receptor, lysozyme in complex with antagonist			
		PDB Id:	3NYA			
		Ligand:	alprenolol			
		Resolution:	3.16Å			
		Species:	Human			
		References:	264			










Agonists						
Key to terms and symbols		View all chemical structures		Click column headers to sort		
Ligand		Sp.	Action	Affinity	Units	Reference
salmeterol		Hs	Full agonist	8.8	pK <sub>i</sub>	136
fenoterol		Hs	Full agonist	6.9	pK <sub>i</sub>	159
isoprenaline		Hs	Full agonist	6.4	pK <sub>i</sub>	123
dobutamine		Hs	Partial agonist	6.2	pK <sub>i</sub>	160
(±)-adrenaline		Hs	Full agonist	6.2	pK <sub>i</sub>	159
salbutamol		Hs	Partial agonist	5.8 – 6.1	pK <sub>i</sub>	133,136
ephedrine		Hs	Partial agonist	5.6	pK <sub>i</sub>	159
terbutaline		Hs	Partial agonist	5.6	pK <sub>i</sub>	136
noradrenaline		Hs	Full agonist	5.4	pK <sub>i</sub>	160

Figure 1. Part of the  $\beta$ 2-adrenoceptor database page showing the 3D structure along with an expert-selected set of receptor agonists.

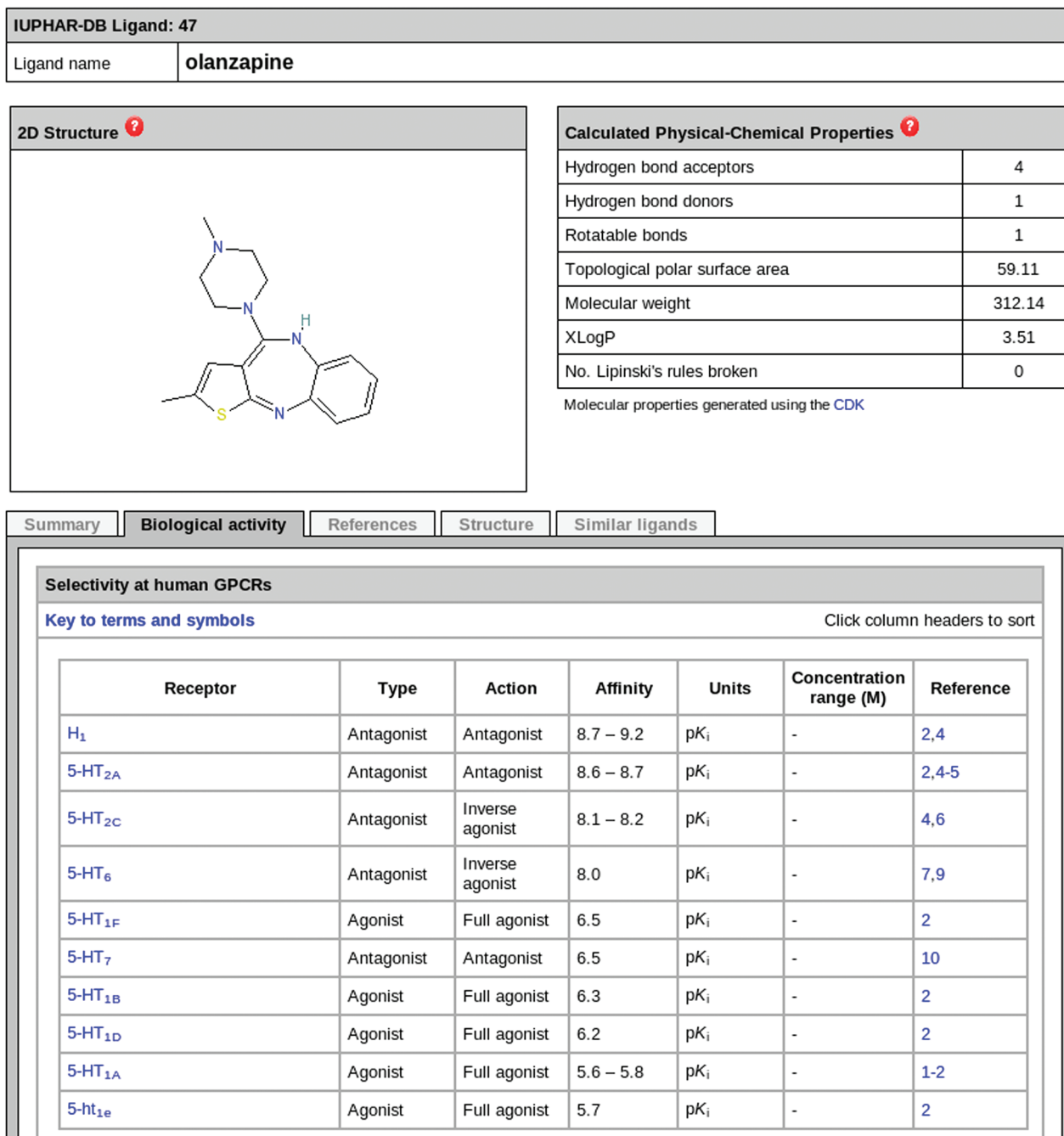
IUPHAR-DB has been developed with these principles strongly in mind. Thus, as the concept of “drug target” gradually evolves, so the database is constantly evaluated, revised, and shaped by the scientific community. Presently, the database includes the products of over 600 human genes (and their rodent orthologs) from four superfamilies: G protein-coupled receptors (GPCRs), nuclear hormone receptors (NHRs), and voltage- and ligand-gated ion channels.<sup>11</sup> Members of these protein families constitute the targets of at least a third of licensed therapeutic drugs, as well as several drugs of abuse.<sup>12</sup> IUPHAR-DB also lists proteins with sequence/structural similarities to known receptors but which do not yet have identified endogenous ligands (such as orphan GPCRs), which may nonetheless be of interest as drug targets. The NC-IUPHAR Evolving Pharmacology subcommittee debates the evidence for and issues guidelines on the acceptance of ligand–receptor pairings, with updates broadcast on the Web site.

Information provided on target proteins in IUPHAR-DB covers a diversity of subjects, including the NC-IUPHAR recommended nomenclature, other names found in literature, details of structure, function, expression, clinical relevance, genetic, and splice variants, genetically modified mouse models, ion channel conductance, GPCR signaling mechanisms, NHR target genes, natural ligands, experimental drug tools, and functional assays. Full text search functionality is provided. Most importantly, all data are

linked to their primary references in PubMed as well as to further sources of information, for example, UniProt,<sup>13</sup> Ensembl,<sup>14</sup> Entrez Gene and Protein,<sup>15</sup> OMIM,<sup>16</sup> and ChEMBL.

Central to the target concept is the need for appropriate knowledge and recommendations on endogenous and experimental ligands/drugs. This includes documenting their actions (e.g., agonist, antagonist, allosteric regulator, ion channel blocker, or gating inhibitor) and their wider activity spectrum (cross-reactivity and off-target effects), which is of interest to both drug discovery and basic experimental science. An example of how this information is displayed for the  $\beta$ 2-adrenoceptor can be seen in Figure 1.

IUPHAR-DB provides curated sets of compounds, their pharmacological actions, and activity data represented as IC<sub>50</sub>, K<sub>i</sub>, K<sub>d</sub>, and EC<sub>50</sub> (as appropriate), linked to their primary literature sources. These include ligands commonly or historically used in experiments, approved drugs, and radio-labeled probes (including 1750 small molecules, 900 peptides, and 80 natural products). Each ligand is represented (where possible) by a common name, synonyms, SMILES strings containing chiral specifications, InChI and InChI Keys, systematic names, and two-dimensional (2D) images. Figure 2 is a screenshot of part of a ligand page showing the bioactivity data and physicochemical properties of the drug olanzapine. Various calculated physicochemical properties are provided, including the five Lipinski



**Figure 2.** Part of the ligand page for the drug olanzapine, displaying the calculated physicochemical properties and a summary of the literature reporting its binding activity at human GPCRs.

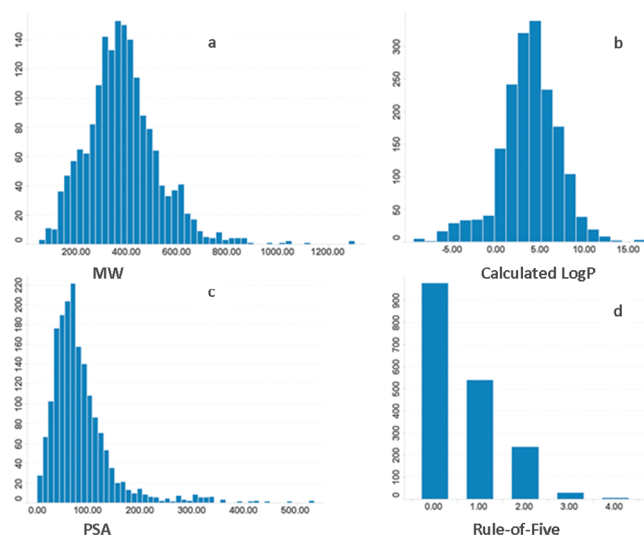
“drug-likeness” measures:<sup>17</sup> polar surface area, predicted LogP, molecular weight, and number of hydrogen bond donors and acceptors. Integrated links provide access to supplementary knowledge in other online resources with biological, chemical, and structural information (e.g., DrugBank,<sup>18</sup> RCSB Protein Data Bank,<sup>19</sup> PubChem, and ChEMBL).

Figure 3 shows that, in terms of their physicochemical profiles, the majority of small molecule compounds in the database obey the Lipinski drug-likeness rules, with greater than 80% of the compounds breaking fewer than two rules.

IUPHAR-DB is widely used as a quick online reference resource for neuroscientists looking for information relevant to

pharmacology and drug discovery. Other useful features include the ability to launch a chemical editor and search tool (from the interactive ligand image or from a link on the page sidebar), allowing structures to be modified and used as queries for structure-based searching. This is the first of a series of planned improvements designed to make the information more accessible. Ongoing work aims to curate the IUPHAR-DB peptide ligands, which remain under-represented in terms of structural properties and searchability. We also intend to broaden the target coverage and to enhance chemical information by providing expert-recommended sets of chemical tools with optimum profiles for practical use in *in vitro* and *in vivo* test systems.





**Figure 3.** Physicochemical properties of the IUPHAR-DB small molecule ligands, indicating the molecular weight (MW) (a), calculated LogP (b), polar surface area (PSA) (c), and Lipinski's rule-of-five (d). The y-axes represent the number of compounds.

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## ABBREVIATIONS

IUPHAR, International Union of Basic and Clinical Pharmacology; NC-IUPHAR, IUPHAR Committee on Receptor Nomenclature and Drug Classification.

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